



Brian Watson
BLIS Technologies Ltd.
81 Glasgow Street
South Dunedin
Dunedin 9012
NEW ZEALAND

Re: GRAS Notice No. GRN 000807

Dear Mr. Watson:

This letter corrects our letter signed on April 18, 2019 sent in response to GRN 000807. The purpose of this letter is to provide revised text about allergen content and allergen labeling.

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000807. We received BLIS Technologies Ltd.'s (BLIS) notice on July 26, 2018, and filed it on September 14, 2018. BLIS submitted an amendment to the notice on November 27, 2018 confirming the absence of biogenic amines and presence of milk allergens in the final product.

The subject of the notice is *Streptococcus salivarius* M18 (*S. salivarius* M18) for use as an ingredient in infant and toddler foods (excluding infant formula); baked goods and baking mixes; beverage and beverage bases; breakfast cereals; cheeses; chewing gum; dairy product analogs; frozen dairy desserts and mixes; gelatins, puddings, and fillings; grain products and pastas; hard candy; whole and skim milk; milk products; nuts and nut products; processed fruits and fruit juices; soft candy; sweet sauces, toppings, and syrups, at a level of 20 mg per serving, providing a minimum of 10^9 colony forming units (CFU) per serving. The notice informs us of BLIS's view that these uses of *S. salivarius* M18 are GRAS through scientific procedures.

BLIS describes the identity and characteristic properties of *S. salivarius* M18 as a spherical, non-motile, Gram-positive bacterium. BLIS states that *S. salivarius* M18 was isolated from the oral cavity of a healthy adult and the strain was deposited with the ATCC under the accession number ATCC BAA 2593. BLIS discusses the results of phenotypic and genotypic characterization used to confirm the strain's identity.

BLIS discusses the manufacturing process for *S. salivarius* M18 by fermentation of a pure culture under controlled conditions. BLIS incorporates into GRN 000807 the general manufacturing process for *S. salivarius* K12 from GRN 000591¹ for the

¹ FDA evaluated GRN 000591 describing uses of *S. salivarius* K12 and responded in letter dated January 2019.
U.S. Food and Drug Administration
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manufacturing of *S. salivarius* M18 as a freeze-dried powder. The growth medium, which contains sucrose, skim milk powder, ammonium salts, and yeast extract, is inoculated with seed culture stock. The culture is then incubated for 16 hours at 33°C. After fermentation, the cell mass is concentrated. The cell concentrate is mixed with a lyoprotectant (i.e., trehalose, lactitol, maltodextrin, and deionized water), and the pH of the suspension is adjusted with ammonium hydroxide or sodium hydroxide. The cell concentrate suspension is then freeze-dried and milled into a powder. The freeze-dried product is packaged and stored at 2 to 8° C. BLIS notes that the final preparation contains some milk residues. BLIS states that all components used in the manufacturing process are food grade and the production is conducted in accordance with current good manufacturing practice.

BLIS provides specifications for *S. salivarius* M18, including a minimum concentration of 10¹¹ CFU/g of *S. salivarius* M18. Specifications also include microbial limits for coliforms (absent in 1 g), *Escherichia coli* (absent in 1 g), *Salmonella* spp. (absent in 25 g), *Staphylococcus aureus* (absent in 1 g), mesophilic aerobic spores (<200 CFU/g), and yeasts and molds (<50 CFU/g). BLIS provides analytical data from three non-consecutive production lots of *S. salivarius* M18 to demonstrate that it can be manufactured to meet these specifications. BLIS states *S. salivarius* M18 is stable at 5±3 °C for up to at least 36 months when packaged and stored correctly.

BLIS estimates the dietary exposure to *S. salivarius* M18 based on the intended uses at a minimum of 10⁹ CFU/serving. BLIS states that the estimated dietary exposures are identical to those described for *S. salivarius* K12 in GRN 000591, as *S. salivarius* M18 will be used in the same food categories and at the same use level. BLIS reports the mean and 90th percentile exposures to *S. salivarius* M18 to be 9.8 x 10⁹ CFU/person(p)/day(d) (2 x 10⁸ CFU/kg body weight (bw)/d) and 1.9 x 10¹⁰ CFU/p/d (4.5 x 10⁸ CFU/kg bw/d), respectively.

BLIS states that *S. salivarius* M18 is closely related to *S. salivarius* K12. BLIS summarizes published animal data and information from GRN 000591 on the safety of *S. salivarius* K12 to support the safety of uses of *S. salivarius* M18. BLIS states that they reviewed the scientific literature through to February 2018. BLIS discusses the results of three clinical studies where *S. salivarius* M18 was administered to healthy children or adults to assess oral health and reports that no serious relevant adverse reactions were observed.

BLIS discusses the data used to support the safety of *S. salivarius* and *S. salivarius* M18. BLIS states that *S. salivarius* has a history of use in dairy fermentation and is listed in the International Dairy Federation inventory of microorganisms with technological beneficial use in food fermentations. BLIS states *S. salivarius* is non-pathogenic and non-toxicogenic. BLIS discusses *S. salivarius* as a rare opportunistic pathogen based on published case reports incorporated from GRN 000591 documenting infections following surgical intervention or in immunocompromised individuals, as well as those identified in an updated literature search performed in March 2018. BLIS states these

25, 2016, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

cases are not relevant to ingestion of *S. salivarius* M18. BLIS discusses unpublished studies demonstrating that *S. salivarius* M18 is susceptible to antibiotics and lacks genes for any major virulence factors or antibiotic resistance.

BLIS includes the statement of a panel of individuals (BLIS's GRAS panel). Based on its review, BLIS's GRAS panel concluded that *S. salivarius* M18 is safe under the conditions of its intended use.

Based on the data and information provided, BLIS concludes that the intended uses of *S. salivarius* M18 are GRAS.

Standards of Identity

In the notice, BLIS states its intention to use *S. salivarius* M18 in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

Potential Labeling Issues

In describing the intended use of *S. salivarius* M18 and in describing the information that BLIS relies on to conclude that *S. salivarius* M18 is GRAS under the conditions of its intended use, BLIS raises a potential issue under the labeling provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Under section 403(a) of the FD&C Act, a food is misbranded if its labeling is false or misleading in any particular way. Section 403(r) of the FD&C Act lays out the statutory framework for the use of labeling claims that characterize the level of a nutrient in a food or that characterize the relationship of a nutrient to a disease or health-related condition. If products that contain *S. salivarius* M18 bear any claims on the label or in labeling, such claims are the purview of the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition. OFAS neither consulted with ONFL on this labeling issue nor evaluated the information in your notice to determine whether it would support any claims made about *S. salivarius* M18 on the label or in labeling.

Allergen Labeling

The FD&C Act requires that the label of a food that is or contains an ingredient that contains a "major food allergen" declare the allergen's presence (section 403(w)). The FD&C Act defines a "major food allergen" as one of eight foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans) or a food ingredient that contains protein derived from one of those foods. *S. salivarius* M18 requires labeling under the FD&C Act Because milk residues are present in the final preparation.

Section 301(II) of the FD&C Act

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In our evaluation of BLIS's notice concluding that *S. salivarius* M18 is GRAS under its intended conditions of use, we did not consider whether section 301(ll) or any of its exemptions apply to foods containing *S. salivarius* M18. Accordingly, our response should not be construed to be a statement that foods containing *S. salivarius* M18, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that BLIS provided, as well as other information available to FDA, we have no questions at this time regarding BLIS's conclusion that *S. salivarius* M18 is GRAS under its intended conditions of use. This letter is not an affirmation that *S. salivarius* M18 is GRAS under 21 CFR 170.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 000807 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Michael A.
Adams -S** Digitally signed by
Michael A. Adams -S
Date: 2019.06.06
13:35:09 -04'00'

Dennis M. Keefe, Ph.D.
Director
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